Practical Bioethics In International Research

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Overview

- Why is a “practical approach” needed?
  - Target audience
- What is a “Practical approach” in international research ethics
  - Unique considerations in international research allow anticipation of moral issues
  - The importance of dialogue
- Cases

Why is a "Practical Approach" to IRE needed?

- Most individuals involved in international research are not ethicists.
  - Disclaimer
- Lack of knowledge is not an excuse for unethical research.
- Mastering bioethics basics is essential for researchers to design and conduct ethical research.

Rationale for Practical Approach

Dialogue is a tool for the establishment of norms and guidelines in IRE.

Researchers are essential to constructive dialogue in international research ethics.

Researchers from developed countries can Facilitate colleagues from less developed countries to participation in the dialogue.

Practical Approach to International Research Ethics for Researchers

1. Basic Bioethics: Develop a working knowledge of basic ethical principles, vocabulary, and guidelines relevant to research ethics, e.g. autonomy, beneficence, non-maleficence, DOH, equipoise etc.
2. Recognize moral issues (or possibility of) arising from unique aspects of international research.
3. Develop ability to apply ethical principles and guidelines to your research, e.g. develop a rationale thought process.
4. Participate in meaningful ethical dialogue about experiences derived from work.
5. Know when you need to get an ethics consult.

Application of Practical Approach in Research Ethics

- Assists the researcher in independent thinking and developing a rationale for thought processes and decisions.
  - Many ethical dilemmas evoke strong emotions
    - E.g. Malawi autopsy case
  - Important to think rather than react to ethical issues

Applying the Practical Approach

Helps to participate in a meaningful dialogue and…..

Defend your work….

Not a trivial issue….e.g. Mexican TB study

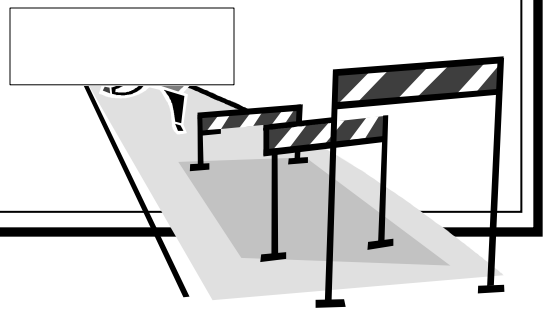
"What! . . . Again?"

First things first… Know the basics in IRE

Know the vocabulary, principles, guidelines, key cases and having an ease with the field of ethics facilitates recognition of ethical issues, dialogue, and is a good antidote to intimidation….

#2 Recognize Potential Ethical Issues Arising from Unique Issues in International Research

1. Medically scarce areas….barriers to medical care
   - Economic: e.g. Mali Potts
   - Expertise: e.g. HIV world wide
   - Access to drugs: approvals, supply, $
   - Long distance to care: problem in many places



Unique Considerations in International Research

2. Vulnerable populations

- Poverty can limit choices, ? autonomy
  - Examples: prostitutes supporting their children
- HIV orphans
- Food scarcity
- Migrant workers: e.g. PNG
- War refugees

Unique Considerations in International Research

3. Cross cultural differences: Different perspectives on simple evaluations
   - E.g. Pregnancy test in China, or Egypt

4. Developed countries have more established medical research than less developed countries (north and south etc)
   - In many LDC's research is not adequately compensated and cannot a full time job, therefore many cases there is less human capital in research
   - Less independent research capacity in LDCs

Unique Considerations in International Research

5. Diseases of interest are often restricted to less developed countries or disproportionately affect these countries, e.g. malaria, HIV, TB, Echinococcosis
   - $$ Little market for diseases that predominately impact on less developed countries. Therefore little pharmaceutical interest and academicians are primary actors in international research
   - Therefore little regulatory expertise.

Unique Considerations in International Research

6. Bioethics as a discipline is relatively new in developed countries and still missing in most of the less developed world.

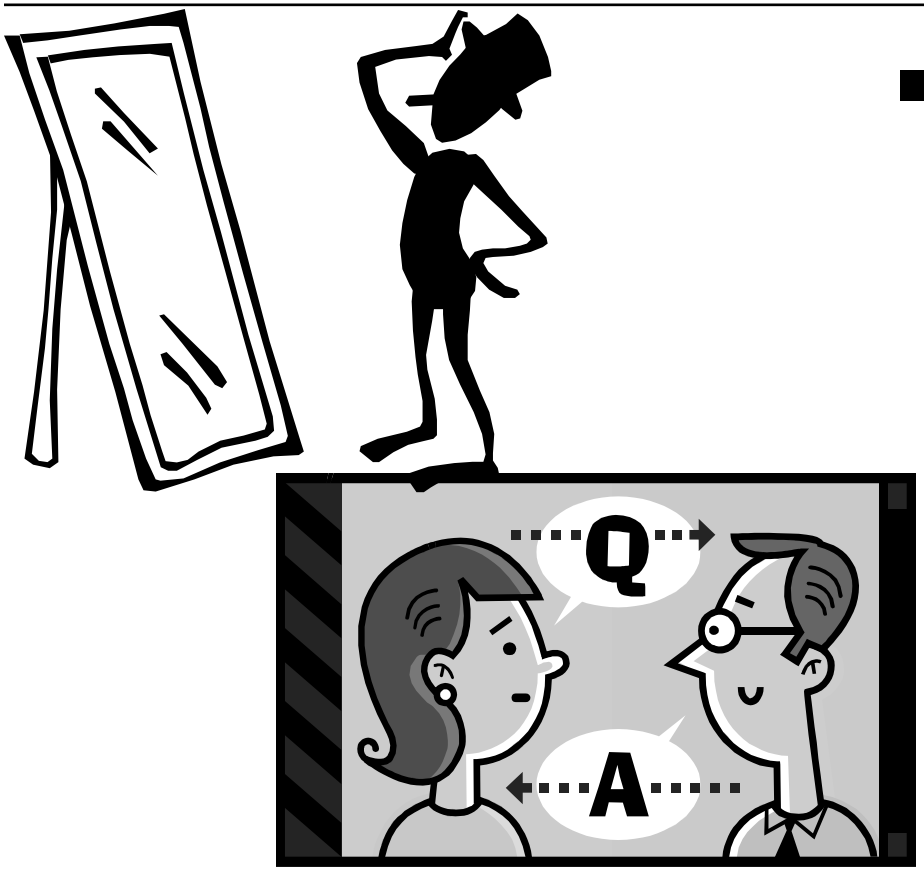
Practical Approach Step 3 Apply Ethics knowledge

- Understand the medical issues (to determine equipoise, understand standard of care, knowledge of local standard of care) and local availability of medical care
- Review unique aspects of research and ask what the moral issues are?
  - Do there seem to be challenges to generally accepted principles? norms? guidelines?
- Read, develop your thoughts and opinions, discuss with others. Document discussions.
- Get help from ethics experts when you need it!

Step 4 Dialogue

- Somewhat analogous to data in medical science
- Exchange of ideas or opinions.
- In research ethics DIALOGUE is the tool through the research community addresses moral dilemmas or identify new areas as potential ethical problems.
- It is critical for all those involved in research to be part of the dialogue as each component of the research team provides a unique perspective

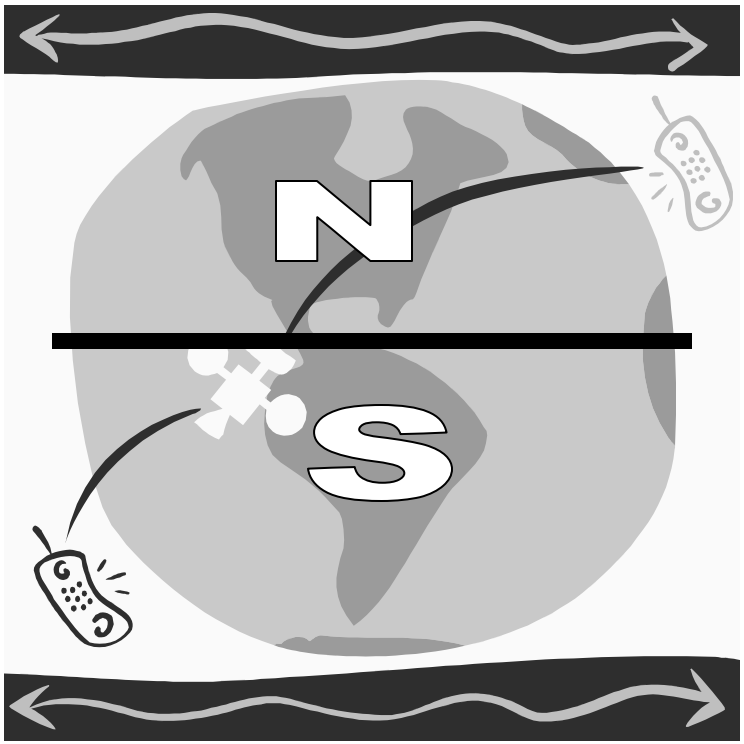
Who Participates in the Dialogue?



- All members of the international research community should participate in the dialogue on research ethics

Dialogue: Bridging the North South Divide

- Bioethics training programs
- Joint papers meetings
- NIH Clinical Bioethics Department, FIC, NIAID, WHO, Wellcome Trust etc contributed towards closing this gap.
- Engage LDC colleagues in international research dialogue.



Case I: Malaria Pathophysiology Study in PNG (1)

- An NIH grant is awarded for the study of the evolution and clinical significance of a genetic variation on red blood cells in Papua New Guinea
- The particular RBC mutation lends protection to *Plasmodium vivax* malaria preventing entry of the parasite in cells which are homozygote for the mutation Df-/Df-.
- The Principal Investigator is not a physician but a well known PhD in the field of malaria genetics.
- The investigator proposes village base active surveillance study to determine if the presence of the mutation changes the time to first infection, disease, and description of severity of disease.

Case 1: Malaria Pathophysiology Study in PNG (2)

- The focus of the study is transmission and disease in *P. vivax* malaria which causes significant morbidity but is not thought to be a major direct contributor to mortality.
- Village case workers to visit houses, interview care providers and determine if children are ill. Children briefly examined in the house including temperature, blood smears for malaria.
- In contrast, *P. falciparum,* also endemic in the study area, is a significant cause of morbidity and mortality particularly in children less than five years of age.

Case 1: Malaria Pathophysiology Study in PNG (3)

- The PNG government is responsible provision of antimalarials through regional health clinics but it is well known that the shelves are often empty.
- At the time of application the government approved regimen for treatment of uncomplicated *P. falciparum* malaria is chloroquine.
- The investigator has been involved with other non-published research which indicated that there is significant prevalence of a resistance mutation to chloroquine the government approved drug commonly used for falciparum malaria.

Case 1: Malaria Pathophysiology Study in PNG (4)

- The research proposal states one PNG physician available for the project in many villages separated by significant distances.
- The investigator suggests children identified as ill, with fever, will be taken by truck to the health care clinic treated with Chloroquine. Children with positive malaria smears who are not ill, e.g. no fever nor symptoms, will not be taken to the health care clinic.
- The investigator maintains the study is not a trial, study personnel will not be providing care for subjects and there will be no adverse events to report in the study. Obligations to study subjects end with transport to the local health care clinics.
- The investigators take no responsibility for caring for ill subjects

Possible Ethical Issues in Case 1

- Medically scarce area
- Qualifications of the investigator? Study team?
- Benefits to the population of the study?
- Obligation to provide care for diseases diagnosed in the study? E.g. deadly *P. falciparum?*
- Obligation to supply antimalarial drugs to health care clinics?
- Obligation to prevent harm because of inadequate treatment?
- Non-interventional study, does this change obligations of investigators?

Case 2 Influenza trial in SEA

- NIH is involved in a multilateral research Network planning to conduct a Double Blinded Randomized Controlled trial comparing two doses of an influenza drug to determine effectiveness in both human and avian influenza with primary virologic endpoint at day 5
- The study will be multicenter study in 3 different countries across 11 different sites in SEA.
- All countries have been involved in clinical trials research but experience with regulatory level studies varies as does Good Clinical Practices, laboratory facilities pharmacy facilities, and training of personnel.
  - None of the hospital labs are accredited.
- Rapid diagnostics for avian influenza are not available at most sites.
- There are no published clinical trials of therapeutics for human avian influenza which provides for equipoise for the current study design. The demand for approved human influenza drugs is greater than supply due to limitations in production supply.
- Some animal data suggests that higher doses for longer periods may be necessary with circulating strain (H5N1).
- H5N1 mortality is approximately 60%

Possible ethical issues in case 2?

- What obligations does the Network have for post trial benefit? To individuals, countries, hospitals?
- What obligations does the sponsor have to the individual sites, investigators, and institutions involved in the study? E.g. training, laboratory capacity
  - Should Network support requested QA/QC of clinical labs?
  - Should Network pay for entire hospital stay of enrolled subjects even after data collection ends?
- Intellectual property issues around samples?

Case #3

- The NIH is working collaboratively with the government of an African Country on a large multicenter HIV trial. The collaboration is jointly managed, though primarily funded by NIH. The centerpiece of the collaboration is a large multicenter trail of antiretroviral therapy.
- There is a prevalent belief in the country that natural products are effective and in some cases more effective than antiretroviral therapy. Pharmacies in the hospital system where the study is being conducted have two products which are combination nutritional therapies on the formulary and many of these products are utilized by the subjects in the clinical trial.

Case #3 (2)

- There have been a few nonrandomized trials evaluating the efficacy of these products with mixed results. There is significant desire from the foreign collaborators to study neutricueticals for the treatment of HIV in the context of the joint research program. Hypoxis, known locally as African Potato, is a natural product found in several products available through in pharmacies throughout the country. There is one product in particular that is widely used in the country which contains the active product Hypoxis. Some researchers in North America have conducted some pharmacokinetic studies on the product and found that is can potentially interfere with antiretroviral therapy. In some animal models there is a suggestion of liver toxicity. Yet the product is widely utilized within the country for HIV/AIDS patients. A study of the safety and efficacy of the product in HIV positive patients on and off therapy could provide guidance for the government and regulatory agencies. Yet preliminary data indicated there may be safety and efficacy concerns.

Ethical Issues in Case #3

- Should an RCT of hypoxis be done?
- What are the moral issues around the study of hypoxis for HIV positive patients?
- Would proceeding with the study conflict with the Principle of Nonmaleficence?
- Would not proceeding with the study violate the autonomy of NIH's African partner?

Case #4 Kenya

- Non-interventional study in Kenya to study the impact of maternal infection and immunity to various parasites (schistosomiasis, malaria) on their offspring. Babies were followed for subsequent acquisition of immunity to these parasites. N=300 mother infant pairs.
- Multiple levels of scientific and ethical review
  - Grant 141 by NIH study section, protocol approved by US university IRB and Kenyan IRB.
  - Once diagnosed with parasites mother's and babies were referred to public health clinic.

Case #4 Kenya (2)

- Published studies at the time demonstrated 30% HIV prevalence in Kenyan women attending antenatal clinics in area of proposed study.
- Single dose Neviripine had been shown to be safe and effective in reducing perinatal HIV transmission. Not available to Kenyan women yet.
- With 300 infants, 30% maternal prevalence, anticipated 90 HIV + moms, anticipate 18-27 HIV infected babies.
- Single dose NVP could be expected to prevent 11-20 HIV infections in infants in the study.

Case #4 Kenya (3)

- Is there a AC responsibility to provide NVP?
- Is ethical responsibility for the AC need mitigated by absence of intervention?
- Investigator willing, he needed $ to purchase NVP.
- Was NIAID morally responsible for this AC need?
- If there is a moral obligation to provide AC how is it conferred?

Case #5 IRB Support in an African Country

- African institution has longstanding research relationship with US investigator.
- Over time US investigator facilitates development of institutional IRB and ethics training program at the African University in part through NIH support.
- Once established the IRB decides it will only review protocols if IRB receives 10% of the amount of the grant.

Case #5 IRB Support in an African Country

- How should the investigator proceed?
- Are the IRB demands unethical?
- Should IRB's be compensated for review?
- How should local IRBs be supported if no fiscal resources are locally available?
- What moral obligations exist towards IRBs?

Summary

- Researchers must develop a practical approach to international research ethics.
  - know basic principles, guidelines, and common vocabulary for international research ethics.
  - Anticipate the ethical and moral issues while designing research and developing research partnerships.
  - Understand unique aspects of international research
- The researcher is an essential part of the international dialogue
  - Dialogue is a tool for the establishment of norms and guidelines.
- Researchers must be prepared to defend the ethical reasoning behind design and conduct issues.
- Expect to be challenged and answer with dialogue. Don't take it personally.
- Get expert ethics consult when you need one!

Thank you

- Thank the Clinical Bioethics Staff for including a “non ethicist” in the course.
- Thank you for your time and attention.